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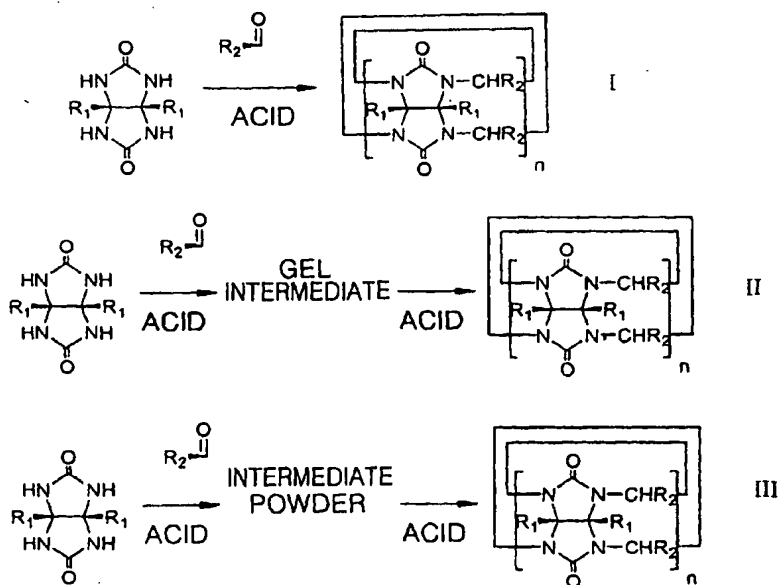
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[Continued on next page]

(54) Title: INCLUSION COMPOUND COMPRISING CUCURBITURIL DERIVATIVES AS HOST MOLECULE AND PHARMACEUTICAL COMPOSITION COMPRISING THE SAME



(57) Abstract: The present invention provides an inclusion compound having a cucurbituril derivative of the formula 1 as a host molecule and a metal complex of the formula 2 as a guest molecule. A pharmaceutical composition having an anticancer effect can be obtained by using the inclusion compound according to the present invention. The pharmaceutical composition can prevent effective components from being biologically degraded in vivo and can exhibit continuous drug effect for a long time just by a single dosage by controlling the release time of the platinum complex once it reaches target tumor cells.

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INCLUSION COMPOUND COMPRISING CUCURBITURIL DERIVATIVES AS HOST MOLECULE AND PHARMACEUTICAL COMPOSITION COMPRISING THE SAME

5 Technical Field

The present invention relates to an inclusion compound and pharmaceutical composition containing the same.

Background Art

10 Numerous anticancer agents using platinum complexes have been synthesized since the discovery of the anticancer effect of platinum complexes. However, the anticancer agents hitherto synthesized have not been satisfactory in view of pharmaceutical efficacy and remain open for improvement in their toxicity and solubility.

15 Currently, cisplatin which is known as one of effective anticancer agents that are widely used, is particularly effective for treatment of ovarian cancer or testicular cancer and is very contributable to treatment of various kinds of cancers. However, since cisplatin has extremely poor water-soluble and organic-soluble properties in itself, it cannot be easily administered, suggesting limitation in the use thereof. Also, cisplatin
20 disadvantageously has serious toxicity. Attempts to overcome such drawbacks of cisplatin, various anticancer agents are under development, and several thousands of anticancer agents have been synthesized. Some of the synthesized anticancer agents are under clinical trials.

Carboplatin is less toxic than cisplatin, and can be administered to patients in a
25 larger amount, that is, approximately of 2000 mg/dose. However, carboplatin is only effective in treatment of tumor cells resistant to cisplatin, and can only be administered intravenously.

Recently, two platinum complexes have been restrictively authorized as anticancer agents; (trans-L-diaminocyclohexane)oxalatoplatinum (II) (oxaliplatin or
30 L-OHP); and cis-diammine-glycolato-O,O'-platinum (II) (nedaplatin or 254-S). The former platinum complex is currently being used for secondary treatment of metastatic colorectal cancer in Japan and France, while the latter one is authorized to be

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commercially available in Japan.

However, in clinical testing, oxaliplatin or nedaplatin demonstrated no distinctive efficacy than cisplatin or carboplatin. Only oxaliplatin exhibited potentiality to be used for treatment of tumors resistant to cisplatin in all clinical trials. Research into platinum complexes having enhanced anticancer effects is continuously carried out, with the aim of development of platinum complexes that are less toxic, capable of administering orally and free of cross resistance to cisplatin and carboplatin.

Existing platinum complex anticancer agents have limitation in improvement of pharmaceutical efficacy by modifying ligand bonded to platinum, and have much room for improvement in view of chemical stability and oral administration.

A novel inclusion compound having 1,1-cyclobutanedicarboxylated diamine platinum (II) (also called "carboplatin") included in alpha-cyclodextrine has been reported. This compound is characterized in that it has a function of increasing water solubility of a platinum complex used as an anticancer agent. However, since a binding constant between alpha-cyclodextrine and carboplatin is low, the binding energy between the two compounds. The inclusion compound is known to have little difference in anticancer effect compared to the case of using only carboplatin.

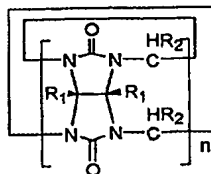
Disclosure of the Invention

An object of the present invention is to provide inclusion compounds having metal complexes such as platinum complexes as a guest molecule, and preparation methods thereof.

It is another object of the present invention to provide pharmaceutical composition containing the inclusion compounds.

The present invention provides an inclusion compound having a cucurbituril derivative of the formula 1 as a host molecule and a metal complex of the formula 2 as a guest molecule:

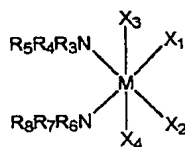
<Formula 1>



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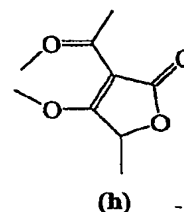
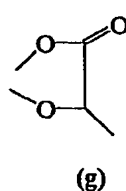
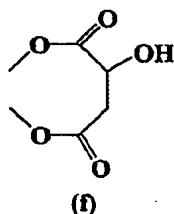
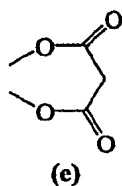
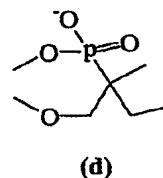
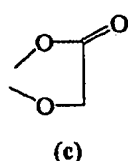
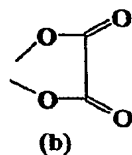
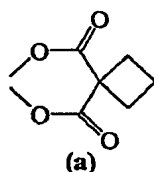
<Formula 2>



- 5 wherein R_1 and R_2 are independently selected from the group consisting of H, C_1 - C_{30} alkyl, C_1 - C_{30} alkene, C_1 - C_{30} alkyne, C_1 - C_{30} alkylthio, C_1 - C_{30} alkylcarboxy, C_1 - C_{30} alkylhydroxy, C_1 - C_{30} alkylsilyl, C_1 - C_{30} alkyloxy, C_1 - C_{30} haloalkyl, nitro, C_1 - C_{30} alkylamine, amine, C_6 - C_{30} unsubstituted cycloalkyl or C_5 - C_{30} cycloalkyl having a hetero atom, and C_6 - C_{15} unsubstituted aryl or C_5 - C_{15} aryl having a hetero atom, n is an integer from 4 to 10 20, M is a divalent or quaternary metal ion selected from the group consisting of transition metals, lanthanide metals, actinide metals, alkali metals and alkali earth metals, X_1 and X_2 meet one selected from the following conditions (i) and (ii):

(i) X_1 and X_2 are independently selected from the group consisting of halogen atom, C_1 - C_{30} haloalkyl, hydroxy, C_1 - C_{30} alkylcarboxy, and C_1 - C_{30} alkyldicarboxy; or

- 15 (ii) X_1 and X_2 are interconnected to each other and are one among components represented by the structural formulas (a) through (h):



X_3 and X_4 meet one selected from the following conditions (i) and (ii):

- 20 (i) when M is a divalent metal ion, X_3 and X_4 denote non-bonding; or
 (ii) when M is a quaternary metal ion, X_3 and X_4 are independently selected from the group consisting of halogen atom, C_1 - C_{30} haloalkyl, hydroxy, C_1 - C_{30} alkylcarboxy,

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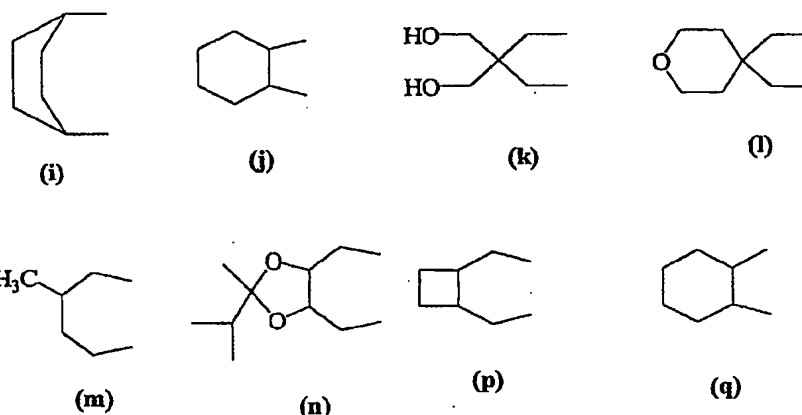
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and C₁-C₃₀ alkyldicarboxy,

R₃, R₄, R₅, R₆, R₇ and R₈ meet one selected from the following conditions (i), (ii) and (iii):

(i) R₃, R₄, R₅, R₆, R₇ and R₈ are independently selected from the group consisting of H, C₁-C₃₀ alkyl, C₁-C₃₀ alkene, C₁-C₃₀ alkyne, C₁-C₃₀ alkylthio, C₁-C₃₀ alkylcarboxy, C₁-C₃₀ alkylhydroxy, C₁-C₃₀ alkylsilyl, C₁-C₃₀ alkyloxy, C₁-C₃₀ haloalkyl, nitro, C₁-C₃₀ alkylamine, amine, C₆-C₃₀ unsubstituted cycloalkyl or C₅-C₃₀ cycloalkyl having a hetero atom, and C₆-C₁₅ unsubstituted aryl or C₆-C₁₅ aryl having a hetero atom;

(ii) R₃, R₄, R₇ and R₈ are independently selected from the group consisting of H, C₁-C₃₀ alkyl, C₁-C₃₀ alkene, C₁-C₃₀ alkyne, C₁-C₃₀ alkylthio, C₁-C₃₀ alkylcarboxy, C₁-C₃₀ alkylhydroxy, C₁-C₃₀ alkylsilyl, C₁-C₃₀ alkyloxy, C₁-C₃₀ haloalkyl, nitro, C₁-C₃₀ alkylamine, amine, C₆-C₃₀ unsubstituted cycloalkyl or C₅-C₃₀ cycloalkyl having a hetero atom, and C₆-C₁₅ unsubstituted aryl or C₆-C₁₅ having a hetero atom, and R₅ and R₆ are interconnected to each other and one among components represented by the structural formulas (i) through (q):



and

(iii) R₃, R₄ and R₈ are independently selected from the group consisting of H, C₁-C₃₀ alkyl, C₁-C₃₀ alkene, C₁-C₃₀ alkyne, C₁-C₃₀ alkylthio, C₁-C₃₀ alkylcarboxy, C₁-C₃₀ alkylhydroxy, C₁-C₃₀ alkylsilyl, C₁-C₃₀ alkyloxy, C₁-C₃₀ haloalkyl, nitro, C₁-C₃₀ alkylamine, amine, C₆-C₃₀ unsubstituted cycloalkyl or C₅-C₃₀ cycloalkyl having a hetero atom, and C₆-C₁₅ unsubstituted aryl or C₆-C₁₅ aryl having a hetero atom, and R₅ and R₆, and R₇ are interconnected to each other and represented by the structural formula (o)

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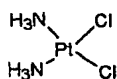
wherein asterisk denotes a position bonded with N:



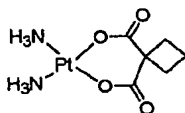
(o)

In the inclusion compound, the binding ratio of the compound of the formula 1 to the metal complex of the formula 2 is preferably in the range of 1:1 to 1:8. In the compound of the formula 1, R_1 is hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, phenyl or pyridyl, R_2 is hydrogen, propyl, phenyl, trichloromethyl, trifluoromethyl, parafluoromethyl or α , α , α -trifluorotolyl, n is preferably an integer from 5 to 8, and the compound of the formula 2 is represented by formulas 4 through 27:

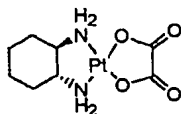
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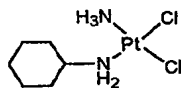
<Formula 5>



<Formula 6>



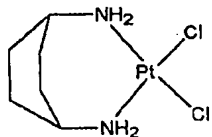
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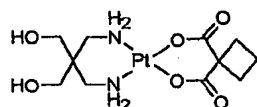
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<Formula 8>



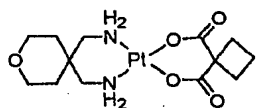
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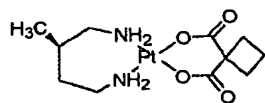
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<Formula 10>

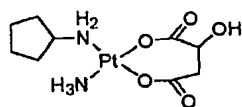


<Formula 11>

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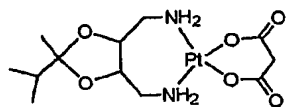


<Formula 12>



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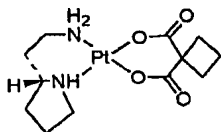
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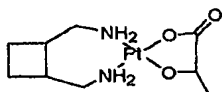
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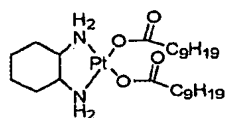
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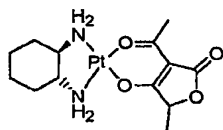
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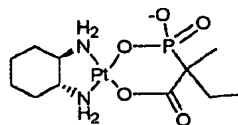


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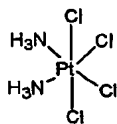


<Formula 18>



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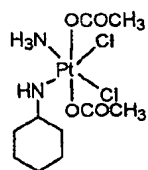
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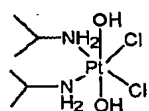
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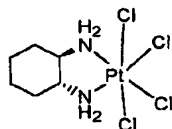
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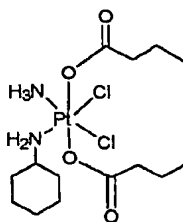
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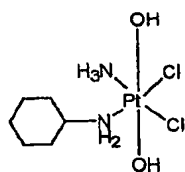


<Formula 23>

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<Formula 24>

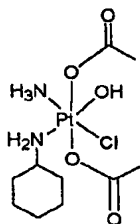


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<Formula 25>

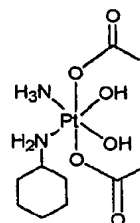
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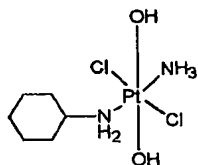


<Formula 26>

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<Formula 27>



10

According to another aspect of the present invention, there is provided a method of preparing the inclusion compounds including reacting a cucurbituril derivative of the formula 1 with a metal complex of the formula 2.

15 In the present invention, the reacting step is performed at room temperature in the presence of a water solvent and includes adding an alcoholic solvent to the resultant product to separate a precipitate. Or, the reacting step is performed at a hydrothermal reactor at a temperature of 80 to 200°C, followed by cooling down to room temperature to separate a crystalline material.

20 According to still another aspect of the present invention, there is provided a pharmaceutical composition comprising the inclusion composition. Here, The pharmaceutical composition is used for treatment of cancer when the inclusion composition comprises the cucurbituril derivative of the formula 1 as a host molecule

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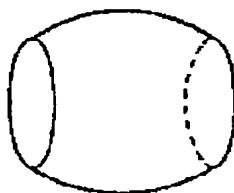
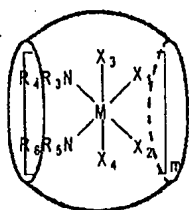
and a metal complex represented by the formulas 4 through 27 as a guest molecule.

The inclusion compound of the present invention is represented by the formula

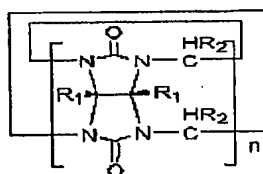
3.

<Formula 3>

5



=



formula 1

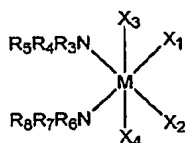
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where,

wherein m is an integer from 1 to 8,

15

<Formula 2>



20

wherein R_1 and R_2 are independently selected from the group consisting of H, C_1 - C_{30} alkyl, C_1 - C_{30} alkene, C_1 - C_{30} alkyne, C_1 - C_{30} alkylthio, C_1 - C_{30} alkylcarboxy, C_1 - C_{30} alkylhydroxy, C_1 - C_{30} alkylsilyl, C_1 - C_{30} alkylloxy, C_1 - C_{30} haloalkyl, nitro, C_1 - C_{30} alkylamine, amine, C_6 - C_{30} unsubstituted cycloalkyl or C_5 - C_{30} cycloalkyl having a hetero atom, and C_6 - C_{15} unsubstituted aryl or C_6 - C_{15} aryl having a hetero atom, n is an integer from 4 to 20, M is a divalent or quaternary metal ion selected from the group consisting of transition metals, lanthanide metals, actinide metals, alkali metals and alkali earth metals, X_1 and X_2 meet one selected from the following conditions (i) and (ii):

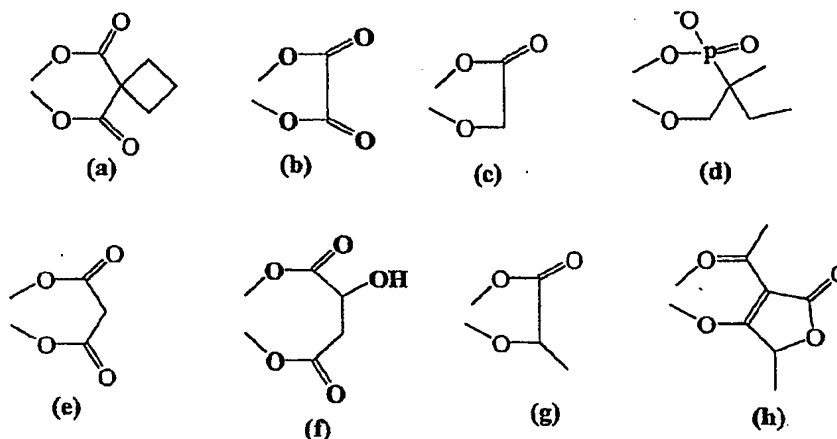
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(i) X_1 and X_2 are independently selected from the group consisting of halogen atom, C_1 - C_{30} haloalkyl, hydroxy, C_1 - C_{30} alkylcarboxy, and C_1 - C_{30} alkyldicarboxy; or

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(ii) X_1 and X_2 are interconnected to each other and are one among components represented by the structural formulas (a) through (h):



5 X_3 and X_4 meet one selected from the following conditions (i) and (ii):

(i) when M is a divalent metal ion, X_3 and X_4 denote non-bonding; or

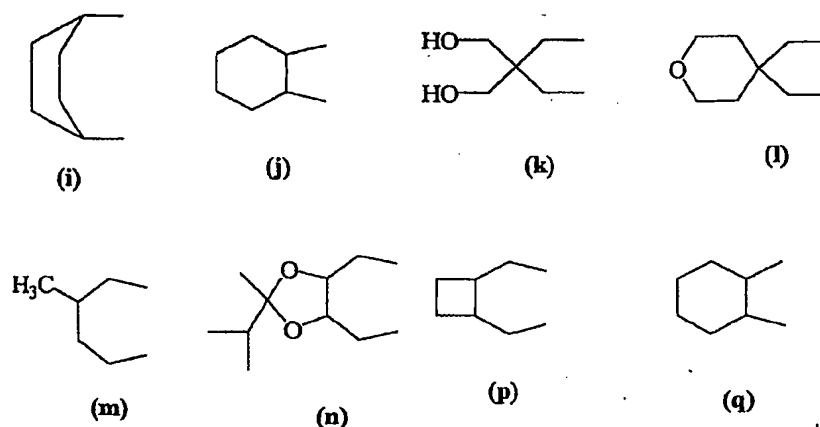
(ii) when M is a quaternary metal ion, X_3 and X_4 are independently selected from the group consisting of halogen atom, C_1 - C_{30} haloalkyl, hydroxy, C_1 - C_{30} alkylcarboxy, and C_1 - C_{30} alkyldicarboxy, R_3 , R_4 , R_5 , R_6 , R_7 and R_8 meet one selected from the following conditions (i), (ii) and (iii):

(i) R_3 , R_4 , R_5 , R_6 , R_7 and R_8 are independently selected from the group consisting of H, C_1 - C_{30} alkyl, C_1 - C_{30} alkene, C_1 - C_{30} alkyne, C_1 - C_{30} alkylthio, C_1 - C_{30} alkylcarboxy, C_1 - C_{30} alkylhydroxy, C_1 - C_{30} alkylsilyl, C_1 - C_{30} alkyloxy, C_1 - C_{30} haloalkyl, nitro, C_1 - C_{30} alkylamine, amine, C_6 - C_{30} unsubstituted cycloalkyl or C_5 - C_{30} cycloalkyl having a hetero atom, and C_6 - C_{15} unsubstituted aryl or C_6 - C_{15} aryl having a hetero atom;

(ii) R_3 , R_4 , R_7 and R_8 are independently selected from the group consisting of H, C_1 - C_{30} alkyl, C_1 - C_{30} alkene, C_1 - C_{30} alkyne, C_1 - C_{30} alkylthio, C_1 - C_{30} alkylcarboxy, C_1 - C_{30} alkylhydroxy, C_1 - C_{30} alkylsilyl, C_1 - C_{30} alkyloxy, C_1 - C_{30} haloalkyl, nitro, C_1 - C_{30} alkylamine, amine, C_6 - C_{30} unsubstituted cycloalkyl or C_5 - C_{30} cycloalkyl having a hetero atom, and C_6 - C_{15} unsubstituted aryl or C_6 - C_{15} having a hetero atom, and R_5 and R_6 are interconnected to each other and one among components represented by the structural formulas (i) through (q):

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and

- (iii) R_3 , R_4 and R_8 are independently selected from the group consisting of H, C_1 - C_{30} alkyl, C_1 - C_{30} alkene, C_1 - C_{30} alkyne, C_1 - C_{30} alkylthio, C_1 - C_{30} alkylcarboxy, C_1 - C_{30} alkylhydroxy, C_1 - C_{30} alkylsilyl, C_1 - C_{30} alkyloxy, C_1 - C_{30} haloalkyl, nitro, C_1 - C_{30} alkylamine, amine, C_6 - C_{30} unsubstituted cycloalkyl or C_5 - C_{30} cycloalkyl having a hetero atom, and C_6 - C_{15} unsubstituted aryl or C_6 - C_{15} aryl having a hetero atom, and R_5 and R_6 , and R_6 and R_7 are interconnected to each other and represented by the structural formula (o) wherein asterisk denotes a position bonded with N:



In the formula 3, the binding ratio of the cucurbituril derivative of the formula 1 to the metal complex of the formula 2 is in the range of 1:1 to 1:8, preferably 1:1 to 1:4.

- The inclusion compound of the formula 3 is presumably maintained at a stable state such that hydrogen atoms bonded to nitrogen atoms included in the metal complex of the formula 2 form hydrogen bonds with oxygen atoms of the cucurbituril derivative, and hydrophobic substituents bonded to nitrogen atoms in the metal complex of the formula 2 are positioned in hydrophobic cavities.

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The preparation of the cucurbituril derivative of the formula 1 was improved by the applicant of the present invention to synthesize and separate cucurbit[6]uril and its homologue cucurbitu[n]uril (n=5, 7 and 8), which was confirmed by X-ray crystal structure determination (U.S. Patent No. 6,365,734). According to this procedure, unlike the conventional separation method in which only hexametric cucurbituril was separated, pentametric, heptametric and octametric cucurbiturils can be separated, thereby selecting a host molecule according to the size of a guest molecule.

In the formulas 1 and 2, examples of the C₁-C₃₀ alkyl in R₁, R₂, R₃, R₄, R₅ and R₆, include methyl, ethyl, propyl, isopropyl and tert-butyl, examples of the C₁-C₃₀ alkenyl include propylene and butene, examples of the C₁-C₃₀ alkynyl include hexynyl, examples of the C₁-C₃₀ alkylthio include butylmethyl sulfide and octanethiol, examples of the C₁-C₃₀ alkylcarboxyl include carboxypropyl and carboxybutyl, examples of the C₁-C₃₀ hydroxyalkyl include hydroxybutyl and hydroxyethyl, examples of the C₁-C₃₀ alkylsilyl include allyltriethylsilyl and vinyltriethylsilyl, examples of the C₁-C₃₀ alkoxy include methoxy and ethoxy, examples of the C₁-C₃₀ haloalkyl include CF₃ and CH₂Cl, examples of the C₁-C₃₀ aminoalkyl include 2-aminobutyl and 1-aminobutyl, examples of the C₅-C₃₀ unsubstituted cycloalkyl include cyclohexyl and cyclopentyl, examples of the C₅-C₃₀ cycloalkyl having a hetero atom include piperidyl and tetrahydrofuranyl, examples of C₆-C₃₀ unsubstituted aryl include phenyl, benzyl and naphthyl, and examples of C₆-C₃₀ aryl having a hetero atom include pentafluorophenyl or pyridyl. In X₁, X₂, X₃ and X₄, examples of the halogen atom include Br, Cl, I and F, examples of the C₁-C₃₀ haloalkyl include bromomethyl and chloromethyl, examples of the C₁-C₃₀ alkylcarboxyl include CH₃C(=O)O-, and example of C₁-C₃₀ alkyldicarboxy include oxalato and malonato.

In M, examples of the transition metal include Pt, Pd and Au, examples of the lanthanide metal include Ln, Gd and Ce, examples of the actinide metals include Ac, examples of the alkali metal include Li, Na and K, and examples of the alkali earth metal include Mg and Ca.

The cucurbituril derivatives of the formula 1 is good in solubility in general solvents. In the cucurbituril derivatives of the formula 1, in particular, R₁ is preferably methyl, ethyl, propyl, isopropyl, butyl, isobutyl, phenyl or pyridyl, R₂ is preferably hydrogen, propyl, phenyl, trichloromethyl, trifluoromethyl, parafluoromethyl or α, α,

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α -trifluorotoluy], and n is preferably an integer from 5 to 8. In cucurbituril derivatives of the formula 1, it is more preferable that R_1 and R_2 are both hydrogen and n is in the range from 5 to 8. These compounds have a water-solubility of 1×10^{-1} to 3×10^{-1} M, and have a good solubility in an organic solvent, in particular, in one selected from the group consisting of methanol, ethanol, dimethylsulfoxide, dimethylformamide and acetonitrile, that is, 1×10^{-4} to 1×10^{-2} M.

In the case where M is a divalent platinum ion, and X_3 and X_4 denote non-bonding, examples of the complex of the formula 2 include cisplatin of the formula 4 wherein X_1 and X_2 are both Cl, and R_3 through R_8 are all H, carboplatin of the formula 5 wherein X_1 and X_2 are both Cl, and X_3 and X_4 are represented by the structural formula a, and R_3 through R_8 are all H, oxaliplatin of the formula 6 wherein R_3 , R_4 , R_6 and R_7 are all H, R_5 and R_8 are represented by the structural formula j, and X_1 and X_2 are represented by the structural formula b, JM118 of the formula 7 wherein X_1 and X_2 are both Cl, R_3 , R_4 , R_5 , R_7 and R_8 are all H, and R_6 is represented by the structural formula j, Pt(cis-1,4-dach)Cl₂ of the formula 8 (Here, dach represents 1,2-diaminocyclohexyl or 1,2-diaminocyclohexane) wherein X_1 and X_2 are both Cl, R_3 , R_4 , R_7 and R_8 are all H, and R_5 and R_6 are interconnected to each other and represented by the structural formula i, xeniplatin of the formula 9 wherein X_1 and X_2 are both Cl, R_3 , R_4 , R_7 and R_8 are all H, and R_5 and R_6 are represented by the structural formula k, enloplatin of the formula 10 wherein X_1 and X_2 are interconnected to each other and represented by the structural formula a, R_3 , R_4 , R_7 and R_8 are all H, and R_5 and R_6 are interconnected to each other and represented by the structural formula ℓ , CI-973 of the formula 11 wherein X_1 and X_2 are interconnected to each other and represented by the structural formula m, R_3 , R_4 , R_7 and R_8 are all H, and R_5 and R_6 are interconnected to each other and represented by the structural formula a, cycloplatin of the formula 12 wherein X_1 and X_2 are interconnected to each other and represented by the structural formula f and R_3 , R_4 , R_6 , R_7 and R_8 are all H, and R_5 is cyclopentyl, SKI 2053R of the formula 13 wherein X_1 and X_2 are interconnected to each other and represented by the structural formula c, R_3 , R_4 , R_7 and R_8 are all H, and R_5 and R_6 are represented by the structural formula n, miboplatin of the formula 14 wherein X_1 and X_2 are interconnected to each other and represented by the structural formula a, R_3 , R_4 and R_8 are all H, and R_5 , R_6 and R_7 are represented by the structural formula o,

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5 iobaplatin of the formula 15 wherein X_1 and X_2 are interconnected to each other and represented by the structural formula g, R_3 , R_4 , R_7 and R_8 are all H, and R_5 and R_6 are represented by the structural formula p, L-NDDP of the formula 16 wherein X_1 and X_2 are both C_9H_{19} , R_3 , R_4 , R_7 and R_8 are all H, and R_5 and R_6 are interconnected to each other and represented by the structural formula j, TRK-710 of the formula 17 wherein X_1 and X_2 are interconnected to each other and represented by the structural formula h, R_3 , R_4 , R_7 and R_8 are all H, and R_5 and R_6 are interconnected to each other and represented by the structural formula j, and $Na[Pt(R,R\text{-dach})(MPBA)]$ of the formula 18 wherein X_1 and X_2 are interconnected to each other and represented by the structural
10 formula d, R_3 , R_4 , R_7 and R_8 are all H, and R_5 and R_6 are interconnected to each other and represented by the structural formula j.

In the case where X_3 and X_4 represent various kinds of substituents, examples of the of the complex of the formula 2 include cisdiaminedichloroplatinium (IV) of the formula 19 wherein X_1 , X_2 , X_3 and X_4 are all Cl, R_3 , R_4 , R_5 , R_6 , R_7 and R_8 are all H,
15 JM216 of the formula 20 wherein X_1 and X_2 are both Cl, X_3 and X_4 are both $OC(=O)CH_3$, R_3 , R_4 , R_5 , R_7 and R_8 are all H, and R_6 are cyclohexyl, iprolatin of the formula 21 wherein X_1 and X_2 are both Cl, X_3 and X_4 are both OH, R_3 , R_4 , R_7 and R_8 are all H, R_5 and R_6 are both isopropyl, omaplatin of the formula 22 wherein X_1 , X_2 , X_3 and X_4 are all Cl, R_3 , R_4 , R_5 , R_7 and R_8 are all H, and R_5 and R_6 are interconnected to each other and
20 represented by the structural formula j, JM221 of the formula 23 wherein X_1 and X_2 are both Cl, X_3 and X_4 are both $-OC(=O)CH_2CH_2CH_3$, R_3 , R_4 , R_5 , R_7 and R_8 are all H, and R_6 is cyclohexyl, JM149 of the formula 24 wherein X_1 and X_2 are both Cl, X_3 and X_4 are both OH, R_3 , R_4 , R_5 , R_7 and R_8 are all H, and R_6 is cyclohexyl, JM518 of the formula 25 wherein X_1 is OH, X_2 is Cl, X_3 and X_4 are both $-OC(=O)CH_3$, R_3 , R_4 , R_5 , R_7 and R_8 are all
25 H, and R_6 is cyclohexyl, JM383 of the formula 26 wherein X_1 and X_2 are both OH, X_3 and X_4 are both $-OC(=O)CH_3$, R_3 , R_4 , R_5 , R_7 and R_8 are all H, and R_6 is cyclohexyl, and JM335 of the formula 27 wherein X_1 is NH_3 , X_2 is Cl, X_3 and X_4 are both OH, R_3 , R_4 , R_5 , R_7 and R_8 are both H, and R_6 is cyclohexyl.

Preparation methods of the inclusion compounds of the formula 3 according to
30 the present invention will now be described.

The inclusion compounds of the formula 3 can be obtained by mixing the cucurbituril derivatives of the formula 1 with the metal complexes of the formula 2, followed by stirring and reacting.

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The reaction is carried out by stirring the reactants at room temperature for 1 to 6 hours in the presence of water as a solvent, or reacting in a hydrothermal reactor at 80 to 200 °C, in particular, 100 to 120 °C, for 1 to 3 days and then being allowed to stand at 50 to 70 °C for 1 to 2 days.

5 During the hydrothermal reaction, the reaction is preferably carried out in the above-noted temperature range in view of reactivity. A work-up procedure resulting from the reaction will now be briefly described. After reacting at room temperature, an alcoholic solvent such as methanol or ethanol is added to the reaction product to separate the resultant in the form of precipitate. During the reaction carried out at the
10 hydrothermal reactor, the reaction product is cooled to room temperature to then precipitate in a crystalline form.

In preparing the inclusion compounds of the formula 3, the binding ratio of the cucurbituril derivative of the formula 1 to the metal complex of the formula 2 can be adjusted according to equivalents in consideration of sizes of cavities of cucurbituril.
15 Preferably, 1 to 10 equivalents of the metal complex of the formula 2 is used based on one equivalent of the cucurbituril derivative of the formula 1.

The synthesizing methods of the cucurbituril derivatives of the formula 1, as described in U.S. Patent No. 6,365,734 to the applicant of the present invention, will now be described in more detail.

20 The method for synthesizing the cucurbituril derivatives according to the present invention can be classified into one of three methods, according to the reaction conditions and the state of intermediate products (refer to FIG. 1).

First, an acid is added to glycoluril in an amount of 3 to 7 moles with respect to 1 mole of glycoluril, and mixed. Preferably, the acid is preferably diluted with water or
25 an organic solvent to be 6 to 12 M. Any acid capable of dissolving glycoluril, for example, hydrochloric acid, sulfuric acid, phosphoric acid, acetic acid, nitric acid and a mixtures of these acids, can be used. The organic solvent as an acid diluent may be dimethylsulfoxide, N,N-dimethylformamide, methanol, ethanol, chloroform or an mixture of these solvents.

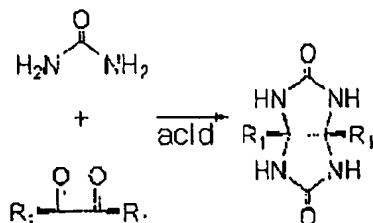
30 The glycoluril can be synthesized by the following method, and can be purchased.

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Urea and glyoxal are dissolved in an aqueous acidic solution or an acid-containing organic solvent, and stirred for a certain period of time. Removal of water or the organic solvent from the reaction mixture produces glycoluril.

<Reaction scheme 1>



Formaldehyde is added to a mixture of the glycoluril and acid for reaction while stirring at 70 to 95°C for 6 to 24 hours. The amount of formaldehyde used is 2 to 20 moles for each mole of glycoluril, but preferably, 4 moles. During the reaction, the color of the reaction solution changes into dark red with time.

The reaction mixture is subjected to a further reaction at 95 to 105°C. The final reaction product varies depending on the reaction temperature and the amount of reactants. The usual final reaction product is a mixture of two or more cucurbituril derivatives, where n is a value from 5 to 20.

Typically, the reaction product is a mixture of 5 to 30% of the cucurbituril derivative with n=5, 30 to 70% of the cucurbituril derivative with n=6, 5 to 30% of the cucurbituril derivative with n=7, 2 to 15% of the cucurbituril derivative with n=8, and 1 to 10% of the cucurbituril derivatives with n=9 to 20.

However, during the reaction at 95 to 105°C, the cucurbituril derivative with n=6 may precipitate in a crystalline form, depending on the reaction temperature, moisture content in the air, and concentration of reactants.

Then, the resulting cucurbituril derivatives are separated from each other by the following fractional crystallization procedure, which will now be described in more detail.

First, the final reaction mixture is diluted with water and left on a bench at room temperature to give the cucurbituril derivative having the formula (1), where n=8. During this separation step, the cucurbituril derivative with n=6 may be formed in a

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crystalline form, and can be easily separated from the cucurbituril derivative with $n=8$ in the formula (1), with a solvent. The solvent for use in the separation of the cucurbituril derivative with $n=6$ may be an alkali metal ion salt solution, such as Na_2SO_4 or K_2SO_4 , an amine-acid salt solution ($\text{H}_2\text{N-R-NH}_2 \cdot 2\text{HCl}$) or a formic acid solution. The
5 crystalline cucurbituril derivative with $n=6$ is soluble in such a solvent, whereas the cucurbituril derivative with $n=8$ is relatively less soluble in the solvent, which enables the separation of the two reaction products.

After separation of the cucurbituril derivative with $n=8$ in the formula (1), the filtrate is further diluted with water and acetone, and filtered. Preferably, water and
10 acetone are added in a ratio of 1:3 to 1:7 by volume. The filtrate after the filtration contains the cucurbituril derivatives having the formula (1), where $n=9$ to 20. Meanwhile, the filter cake is dissolved in water. Here, the cucurbituril derivatives with $n=5$ and 7 in the formula (1) are obtained as a major component of the water soluble fraction. The major component in the water insoluble fraction is the cucurbituril
15 derivative with $n=6$ in the formula (1).

The cucurbituril derivatives with $n=5$ and 7 in the formula (1) can be separated from each other with a mixture of water and methanol in a ratio of 1:0.7 to 1:1.3 by volume. That is, filter cakes were dissolved in water and methanol, and filtered. The insoluble fraction is then recrystallized to obtain the pure crystalline cucurbituril
20 derivative with $n=7$ in the formula (1). Also, the filtrate, which is the water and methanol soluble fraction, is recrystallized with an aqueous solution of acid to obtain the crystalline cucurbituril derivative with $n=5$ in the formula (1).

In the second synthetic method of the cucurbituril derivatives according to the present invention, a relatively small amount of acid than in the previously mentioned
25 method is added to the reaction mixture of glycoluril and formaldehyde to result in an intermediate product in a gel state. Then, the intermediate product is treated with an acid to obtain the cucurbituril derivatives having the formula (1).

In particular, an acid is added to glycoluril in an amount of 0.1 to 1 moles with respect to 1 mole of glycoluril. The acid added may be diluted with water or an
30 organic solvent in the same ratio as in the first method mentioned above.

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Then, 2 to 20 moles, but preferably, 2 to 4 moles, of formaldehyde with respect to 1 mole of glycoluril is added to the mixture, and reacted at 70 to 85°C to obtain the intermediate product in a gel state.

After drying the intermediate product, 3 to 7 moles of an acid with respect to 1 mole of the intermediate product are added and stirred at 70 to 105°C. Here, the acid is diluted with water or an organic solvent prior to the addition.

In the above-described method, the final reaction product slightly varies depending on the reaction temperature and the amount of reactants, as in the first synthesis method. However, the usual final reaction product is a mixture of two or more cucurbituril derivatives in the formula (1), where n is a value from 5 to 20.

Typically, the final reaction product is a mixture of 5 to 30% of the cucurbituril derivative having n=5, 30 to 70% of the cucurbituril derivative having n=6, 5 to 30% of the cucurbituril derivative having n=7, 2 to 15% of the cucurbituril derivative having n=8, and 1 to 10% of the cucurbituril derivatives having n=9 to 20.

Then, the fractional separation is carried out to give the cucurbituril derivatives having the formula (2), where n is a value from 5 to 20, as in the first synthesis method.

The third synthetic method of the cucurbituril derivatives disclosed by the present invention involves a reaction under a high pressure condition, which is different from the two previously mentioned synthetic methods. In this synthetic method, the amount of acid added for the reaction with glycoluril and formaldehyde is reduced, as in the second synthesis method, to produce oligomer powder as an intermediate product.

The obtained intermediate product is treated with an acid to synthesize the cucurbituril derivatives having the formula (1). In contrast to the two previously mentioned methods, the cucurbituril derivative having n=7 is produced in a relatively higher yield, whereas the cucurbituril derivative having n=6 is produced in a relatively lower yield.

The third synthetic method will now be described in particular. Glycoluril, 0.1 to 1 moles of an acid and 2 to 4 moles of formaldehyde are put into a high-pressure reactor.

The acid is diluted with water or an organic solvent prior to use. The concentration of the diluted acid solution may vary depending on the reaction conditions, but preferably, 1 to 12M, more preferably 6 to 12M, of the acid solution is added. Then, the mixture is reacted at 80 to 130°C. Preferably, the reaction is carried out under a pressure of 15 to 100 psi, but preferably, 20 to 80 psi. If the reaction pressure is higher than 100 psi,

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it may place the synthesis process itself into a dangerous situation. Meanwhile, if the reaction pressure is lower than 15 psi, the yield may be low.

After the reaction is completed, the solid reaction product is washed with water or an organic solvent and dried to yield oligomers in powder form as an intermediate
5 product.

Then, 3 to 7 moles of an acid for each mole of oligomers is added to the oligomers, and the mixture is stirred at 70 to 105°C. The acid added herein is diluted with water or an organic solvent, as in the first and second synthesis methods. The concentration and types of the useful acids are also identical to those in the first and
10 second synthesis methods. As a result, a mixture of two or more cucurbituril derivatives, where n is a value from 5 to 20, is obtained as in the first and second synthesis methods.

Typically, the final reaction product is a mixture of 5 to 30% of the cucurbituril derivative having n=5, 30 to 70% of the cucurbituril derivative having n=6, 5 to 30% of
15 the cucurbituril derivative having n=7, 2 to 15% of the cucurbituril derivative having n=8, and 1 to 10% of the cucurbituril derivatives having n=9 to 20.

After the reaction between the oligomers and the acid is completed, the separation procedure is carried out to give the cucurbituril derivatives having the formula (1), where n is a value from 5 to 20, as in the first and second synthesis
20 methods.

The present invention provides easy preparation methods for the cucurbituril derivatives having the formula (1), where n ranges from 5 to 11, and separation methods based on their different solubilities in a common solvent such as water, acetone and an organic solvent such as methanol. Also, according to this procedure,
25 mixtures of at least two selected from the cucurbituril derivatives having the formula (1), where n is a value from 5 to 20. These mixtures can be separated as each cucurbituril derivative by methods shown in FIG. 2.

The pharmaceutical composition according to the present invention includes the inclusion compound of the formula 3. The inclusion compound is contained in the
30 pharmaceutical composition in a pharmaceutically effective amount. In the case of using a platinum complex, e.g., cisplatin, as the metal complex of the formula 2, the inclusion compound can be advantageously used as an anticancer agent. The

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anticancer agent can prevents the platinum complex as an effective component from being biologically degraded in vivo and can exhibit continuous drug effect for a long time just by a single dosage by controlling the release time of the platinum complex once it reaches target tumor cells.

5 The pharmaceutical composition of this invention can be administered to humans or animals orally or non-orally. For example, the inclusion compound dissolved or suspended in an injection solvent such as injection water, a saline solution, 5% glucose aqueous solution, aqueous ethanol, aqueous glycerine or aqueous propylene glycol, in the form of, for example, intravenous injection, intramuscular
10 injection, subcutaneous injection or instillation.

In the pharmaceutical composition of the invention, formulations include tablets, capsules, soft capsules, liquid preparations, powdery preparations and the like. The formulations in the state of a solution or a suspension can be preserved in sealed ampoules or vials, in the form of, for example, granules, powders, microgranules or
15 freeze dried preparations for being dissolved directly before use. A stabilizer may be further added to the formulations.

When the pharmaceutical composition of the invention, including the inclusion compound and metal complexes such as the compounds represented by the formulas 4-27, is administered for treatment of cancer, its daily dose for adult person is
20 substantially the same as that of an anticancer agent, for example, in an amount of approximately 2000 mg/dose, typically once a week or every 3 or 4 weeks, which can be administered orally or non-orally.

The pharmaceutical composition of the invention can be advantageously used for treatment of various types of cancers such as ovarian cancer, breast cancer or
25 colonic cancer.

Various kinds of pharmaceutically acceptable additives can be further added to the pharmaceutical composition according to the invention, and the concentration thereof may vary depending on the addition purposes.

30 Brief Description of the Drawings

FIG. 1 is a schematic diagram showing synthesis mechanism of cucurbituril derivatives of the formula 1;

FIG. 2 is a diagram of the X-ray crystal structure of an inclusion compound

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according to Synthesis Example 1 of the present invention; and

FIG. 3 is a titration graph of the inclusion compound according to Synthesis Example 1 of the present invention, measured by an isothermal microcalorimeter.

5 Best mode for carrying out the Invention

The present invention is illustrated in more detail by the following examples without, however, being limited thereby.

Examples

10 Synthesis Example 1: Synthesis of inclusion compound of oxaliplatin and cucurbitu[7]ril

3 mg of oxaliplatin and 9 mg of cucurbitu[7]ril were added to 20 mL water and hydrothermally reacted at 100°C for 24 hours at a hydrothermal reactor with a reaction vessel made of Teflon. The reaction mixture was slowly cooled down to room temperature to give a colorless, plate-shaped crystalline material. The crystalline material was then filtered and dried in the presence of air, thereby obtaining an inclusion compound at a yield of 61%.

Synthesis Example 2: Synthesis of inclusion compound of oxaliplatin and cucurbitu[7]ril

3 mg of oxaliplatin and 9 mg of cucurbitu[7]ril were added to 20 mL water and reacted, and then ethanol was added to the mixture to form a precipitate. Thereafter, the precipitate was filtered and dried in the presence of air, thereby obtaining an inclusion compound at a yield of 72%.

The inclusion compounds synthesized in Synthesis Examples 1 and 2 were subjected to analysis by NMR (500 MHz), CHNS determination and Mass spectrometry, respectively, and the results thereof are:

¹H NMR (500MHz, D₂O) 2.26(2H, m), 1.96-1.98(2H, m), 1.60-1.62(2H, m), 1.21-1.23(2H, m), 1.07-1.09(2H, m)

Elemental analysis {(C₈H₁₄N₂O₄Pt)(C₄₂H₄₂N₂₈O₁₄)}·8H₂O

Cald. C, 34.87; H, 4.33; N, 24.40

30 Found C, 34.47; H, 4.43; N, 24.65

ESI-MS m/z [M+2Li]²⁺ 786.7 (Cald: 787.3), [M+2Li+DMF]²⁺ 823.3 (Cald: 823.2), [M+Li]⁺ 1566.5 (Cald: 1566.5), [M+Li+LiI]⁺ 1700.5 (Cald: 1700.3), [M+Li+2LiI]²⁺ 1834.4

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(cald: 1834.3), $[M+Li+3LiI]^3+$ 1968.4 (Cald: 1968.1)

Also, the X-ray crystal structure of the inclusion compound was investigated, and the result thereof is shown in FIG. 2. FIG. 2 shows X-ray crystal structure of the inclusion compound, and data thereof are listed below:

5 $C_{50}H_{81.33}N_{30}O_{31.67}Pt$, m/w=1804.54, Orthorhombic, Space group $P2_12_12_1$,
a=23.6543(5), b=30.23670(10), c=31.2827(6), Volume=22374.3(6), $R_1=0.1093$

Referring to FIG. 2, the inclusion compound contains cucurbitu[7]ril as a host molecule and oxaliplatin as a guest molecule, in a binding ratio of 1:1. According to
10 observation of the host-guest molecular structure, an amine atom of the guest molecule, that is, oxaliplatin, was maintained at the same geometric level as an oxygen atom of the host molecule, that is, cucurbituril. Also, a hydrogen bond was established between a hydrogen atom connected to the ammine of oxaliplatin and an oxygen atom of cucurbituril, and the cyclohexyl of the oxaliplatin is encapsulated in a hydrophobic
15 cavity. In such a manner, a stable inclusion compound was formed.

The inclusion compounds synthesized in Synthesis Examples 1 and 2 were subjected to analysis by an isothermal microcalorimeter to measure binding constants of oxaliplatin and cucurbitu[7]ril, and the results thereof are shown in FIG. 3. The experiment was carried out under a constant temperature condition of 25°C, with
20 concentrations of 20 mM oxaliplatin and 1 mM cucurbitu[7]ril.

As a result, oxaliplatin and cucurbituril derivative had a binding constant of $2.39 \times 10^5 (\pm 0.4) M^{-1}$, a binding enthalpy of -6.33 kcal/mole (± 0.07), and entropy of 3.31 esu. Such a relatively high binding constant of oxaliplatin and cucurbituril, compared to $60 M^{-1}$ of Stoddart group, suggests a very strong bond between host-guest
25 molecules. Also, the positive entropy value confirms that the reaction is entropically advantageous as water molecule trapped by the host molecule escapes during a binding process.

Synthesis Example 3: Synthesis of inclusion compound of oxaliplatin and cucurbitu[8]ril

30 13 mg of cucurbitu[8]ril and 3 mg of oxaliplatin were added to 10 mL water and hydrothermally reacted at 100°C for 24 hours, followed by slowly cooling to give a crystalline material. The crystalline material was then filtered, followed by drying in

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the presence of air, thereby obtaining 6 mg of an inclusion compound at a yield of 75%.

Synthesis Example 4: Synthesis of inclusion compound of oxaliplatin and cucurbitu[8]ril

13 mg of cucurbitu[8]ril and 3 mg of oxaliplatin were added to 10 mL water and stirred at room temperature, followed by adding methanol thereto to induce precipitation. The resultant precipitate was filtered and dried in the presence of air, thereby obtaining 6 mg of an inclusion compound at a yield of 78%.

In the inclusion compounds synthesized in Synthesis Examples 3 and 4, oxaliplatin and cucurbitu[8]ril were contained in a binding ratio of 2:1.

Synthesis Example 5: Synthesis of inclusion compound of *cis*-dichloroethylenediamine platinum (II) and cucurbitu[7]ril

3 mg of *cis*-dichloroethylenediamineplatinum (II) and 9 mg of cucurbitu[7]ril were added to 10 mL water and hydrothermally reacted at 100°C, followed by slowly cooling down, filtering and drying in the presence of air, thereby obtaining 5 mg of an inclusion compound at a yield of 65%.

Synthesis Example 6: Synthesis of inclusion compound of *cis*-dichloroethylenediamine platinum (II) and cucurbitu[7]ril

3 mg of *cis*-dichloroethylenediamineplatinum (II) and 9 mg of cucurbitu[7]ril were added to 10 mL water and stirred at room temperature, followed by adding methanol thereto to induce precipitation. The resultant precipitate was filtered and dried in the presence of air, thereby obtaining 5 mg of a solid inclusion compound at a yield of 65%.

Synthesis Example 7: Synthesis of inclusion compound of *cis*-dichloroethylenediamine platinum (II) and cucurbitu[8]ril

3 mg of *cis*-dichloroethylenediamineplatinum (II) and 7 mg of cucurbitu[8]ril were added to 10 mL water and hydrothermally reacted at 100°C for 24 hours. As a result, the resultant crystalline material was filtered and dried in the presence of air, thereby obtaining 5 mg of an inclusion compound at a yield of 68%.

Synthesis Example 8: Synthesis of inclusion compound of *cis*-dichloroethyldiamine platinum (II) and cucurbitu[8]ril

3 mg of *cis*-dichloroethylenediamine platinum (II) and 7 mg of cucurbitu[8]ril were added to 10 mL water and stirred at room temperature. Then, methanol was added to

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the reaction product to form a precipitate.

Thereafter, the precipitate was filtered and dried in the presence of air, thereby obtaining 5 mg of a solid inclusion compound at a yield of 65%.

Anticancer activities of the inclusion compounds synthesized in Synthesis Examples 1 and 2 were measured as follows.

First, the oxaliplatin-cucurbitu[7]ril inclusion compounds synthesized in Synthesis Examples 1 and 2, were freeze-dried to prepare samples. Tumor cells used were A 549 (human non-small cell lung), SKOV-3 (human ovarian), SKMEL-2 (human melanoma), XF-498 (human CNS), and HCT-15 (human colon), and analyzed by SRB (sulforhodamine B) assay. The analysis results are shown in Table 1.

Table 1: Antiproliferative activity ($ED_{50}/\mu M$)

Cell line ^a	Inclusion compounds between oxaliplatin and CB[7] ^b
A549	2.43
SKOV-3	4.88
SKMEL-2	18.71
XF-498	4.94
HCT-15	13.26

a: A549 human non-small cell lungs; SKOV-3 human ovarian; SKMEL-2 human melanoma; XF-498 human CNS; HCT-15 human colon,

b: Good water-solubility

As shown in Table 1, the oxaliplatin-cucurbitu[7]ril inclusion compounds synthesized in Synthesis Examples 1 and 2 exhibited good antiproliferative activities, which is presumably due to strong coordination of oxaliplatin to cucurbitu[7]ril. Also, since the inclusion compounds have capability of slowly releasing oxaliplatin, it was confirmed that continuous drug effect could be exhibited for a long time just by a single dosage of the pharmaceutical composition.

Industrial Applicability

The inclusion compound according to the present invention include a cucurbituril derivative of the formula 1 as a host molecule and a metal complex of the formula 2 as a guest molecule. A pharmaceutical composition having an anticancer effect can be obtained by using the inclusion compound according to the present invention. The pharmaceutical composition can prevent effective components from being biologically degraded in vivo and can exhibit continuous drug effect for a long time just by a single

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dosage by controlling the release time of the platinum complex once it reaches target tumor cells.

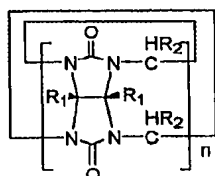
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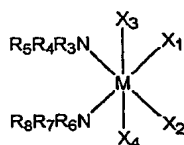
What is claimed is:

1. An inclusion compound having a cucurbituril derivative of the formula 1 as a host molecule and a metal complex of the formula 2 as a guest molecule:

5 <Formula 1>



<Formula 2>



10

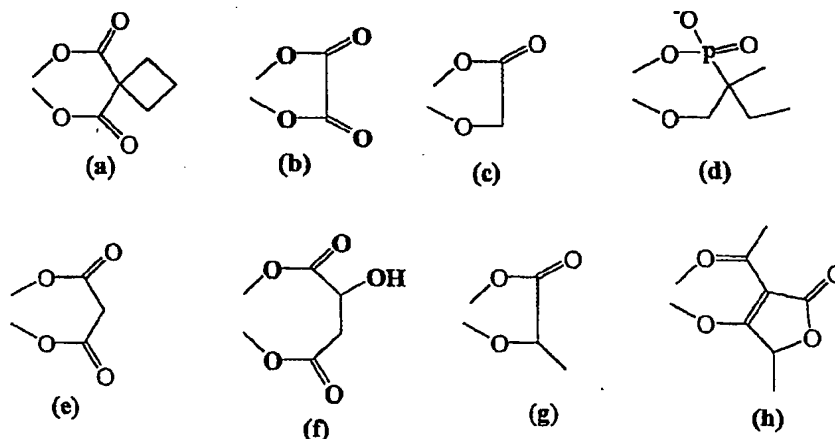
wherein R₁ and R₂ are independently selected from the group consisting of H, C₁-C₃₀ alkyl, C₁-C₃₀ alkene, C₁-C₃₀ alkyne, C₁-C₃₀ alkylthio, C₁-C₃₀ alkylcarboxy, C₁-C₃₀ alkylhydroxy, C₁-C₃₀ alkylsilyl, C₁-C₃₀ alkyloxy, C₁-C₃₀ haloalkyl, nitro, C₁-C₃₀ alkylamine, amine, C₅-C₃₀ unsubstituted cycloalkyl or C₅-C₃₀ cycloalkyl having a hetero atom, and C₆-C₁₅ unsubstituted aryl or C₆-C₁₅ aryl having a hetero atom, n is an integer from 4 to 20, M is a divalent or quaternary metal ion selected from the group consisting of transition metals, lanthanide metals, actinide metals, alkali metals and alkali earth metals, X₁ and X₂ meet one selected from the following conditions (i) and (ii):

(i) X₁ and X₂ are independently selected from the group consisting of halogen atom, C₁-C₃₀ haloalkyl, hydroxy, C₁-C₃₀ alkylcarboxy, and C₁-C₃₀ alkyldicarboxy; or

(ii) X₁ and X₂ are interconnected to each other and are one among components represented by the structural formulas (a) through (h):

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X_3 and X_4 meet one selected from the following conditions (i) and (ii):

(i) when M is a divalent metal ion, X_3 and X_4 denote non-bonding;

5 or

(ii) when M is a quaternary metal ion, X_3 and X_4 are independently selected from the group consisting of halogen atom, C_1 - C_{30} haloalkyl, hydroxy, C_1 - C_{30} alkylcarboxy, and C_1 - C_{30} alkyldicarboxy,

R_3 , R_4 , R_5 , R_6 , R_7 and R_8 meet one selected from the following conditions

10 (i), (ii) and (iii):

(i) R_3 , R_4 , R_5 , R_6 , R_7 and R_8 are independently selected from the group consisting of H, C_1 - C_{30} alkyl, C_1 - C_{30} alkene, C_1 - C_{30} alkyne, C_1 - C_{30} alkylthio, C_1 - C_{30} alkylcarboxy, C_1 - C_{30} alkylhydroxy, C_1 - C_{30} alkylsilyl, C_1 - C_{30} alkyloxy, C_1 - C_{30} haloalkyl, nitro, C_1 - C_{30} alkylamine, amine, C_6 - C_{30} unsubstituted cycloalkyl or C_5 - C_{30} cycloalkyl having a hetero atom, and C_6 - C_{15} unsubstituted aryl or C_6 - C_{15} aryl having a hetero atom;

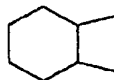
(ii) R_3 , R_4 , R_7 and R_8 are independently selected from the group consisting of H, C_1 - C_{30} alkyl, C_1 - C_{30} alkene, C_1 - C_{30} alkyne, C_1 - C_{30} alkylthio, C_1 - C_{30} alkylcarboxy, C_1 - C_{30} alkylhydroxy, C_1 - C_{30} alkylsilyl, C_1 - C_{30} alkyloxy, C_1 - C_{30} haloalkyl, nitro, C_1 - C_{30} alkylamine, amine, C_6 - C_{30} unsubstituted cycloalkyl or C_5 - C_{30} cycloalkyl having a hetero atom, and C_6 - C_{15} unsubstituted aryl or C_6 - C_{15} aryl having a hetero atom, and R_5 and R_6 are interconnected to each other and one among components represented by the structural formulas (i) through (q):

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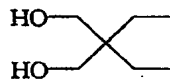
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(i)



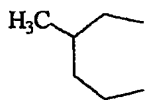
(j)



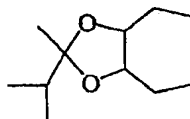
(k)



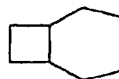
(l)



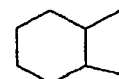
(m)



(n)



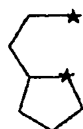
(p)



(q)

and

- 5 (iii) R_3 , R_4 and R_8 are independently selected from the group consisting of H, C_1 - C_{30} alkyl, C_1 - C_{30} alkene, C_1 - C_{30} alkyne, C_1 - C_{30} alkylthio, C_1 - C_{30} alkylcarboxy, C_1 - C_{30} alkylhydroxy, C_1 - C_{30} alkylsilyl, C_1 - C_{30} alkyloxy, C_1 - C_{30} haloalkyl, nitro, C_1 - C_{30} alkylamine, amine, C_6 - C_{30} unsubstituted cycloalkyl or C_5 - C_{30} cycloalkyl having a hetero atom, and
- 10 C_6 - C_{15} unsubstituted aryl or C_6 - C_{15} aryl having a hetero atom, and R_5 and R_6 , and R_6 and R_7 are interconnected to each other and represented by the structural formula (o) wherein asterisk denotes a position bonded with N:



(o)

15

2. The inclusion compound according to claim 1, wherein the binding ratio of the compound of the formula 1 to the metal complex of the formula 2 is in the range of 1:1 to 1:8.

20

3. The inclusion compound according to claim 1, wherein the binding ratio of the compound of the formula 1 to the metal complex of

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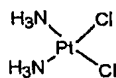
the formula 2 is in the range of 1:1 to 1:4.

4. The inclusion compound according to claim 1, wherein in the compound of the formula 1, R_1 is hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, phenyl or pyridyl, R_2 is hydrogen, propyl, phenyl, trichloromethyl, trifluoromethyl, parafluoromethyl and α , α , α -trifluorotoluy, and n is an integer from 5 to 8.

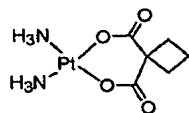
5. The inclusion compound according to claim 1, wherein in the compound of the formula 2, M is one selected from the group consisting of gold (Au), platinum (Pt) and palladium (Pd).

6. The inclusion compound according to claim 1, wherein the compound of the formula 2 is represented by formulas 4 through 27:

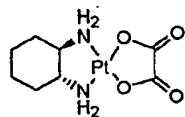
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<Formula 5>



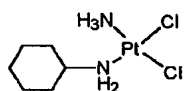
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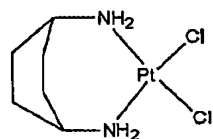
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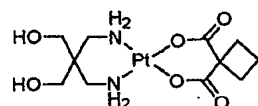


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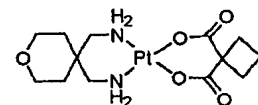
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<Formula 9>



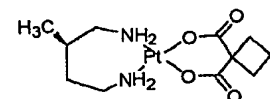
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<Formula 10>



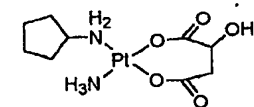
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<Formula 11>



<Formula 12>

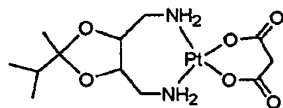
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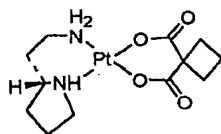
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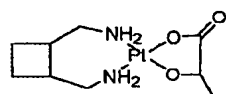


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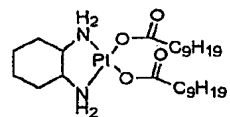
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<Formula 15>



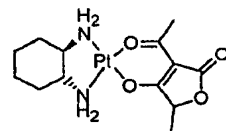
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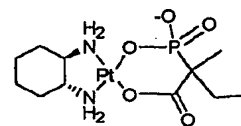
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<Formula 17>



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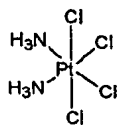
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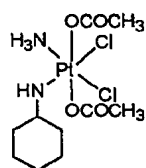
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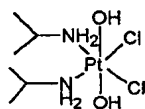


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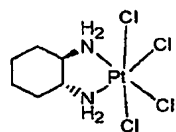
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<Formula 21>



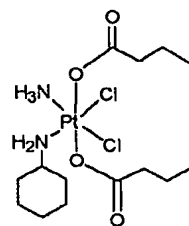
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<Formula 22>



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<Formula 23>

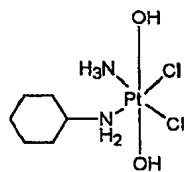


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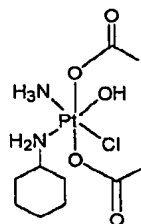
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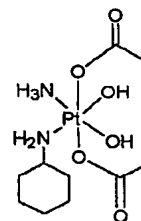


<Formula 25>



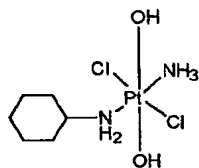
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<Formula 26>



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<Formula 27>



15

7. A method of preparing the inclusion compound according to any one of claims 1 through 6, comprising the step of reacting the cucurbituril derivative of the formula 1 with the metal complex of the formula 2.

20

8. The method according to claim 7, wherein the reacting step

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is performed at room temperature in the presence of a water solvent and includes adding an alcoholic solvent to the resultant product to separate a precipitate.

5 9. The method according to claim 7, wherein the reacting step is performed at a hydrothermal reactor at a temperature of 80 to 200°C, followed by cooling down to room temperature to separate a crystalline material.

10 10. A pharmaceutical composition comprising the inclusion composition according to any one of claims 1 through 6, the inclusion composition comprising the cucurbituril derivative of the formula 1 as a host molecule and a metal complex of the formula 2 as a guest molecule.

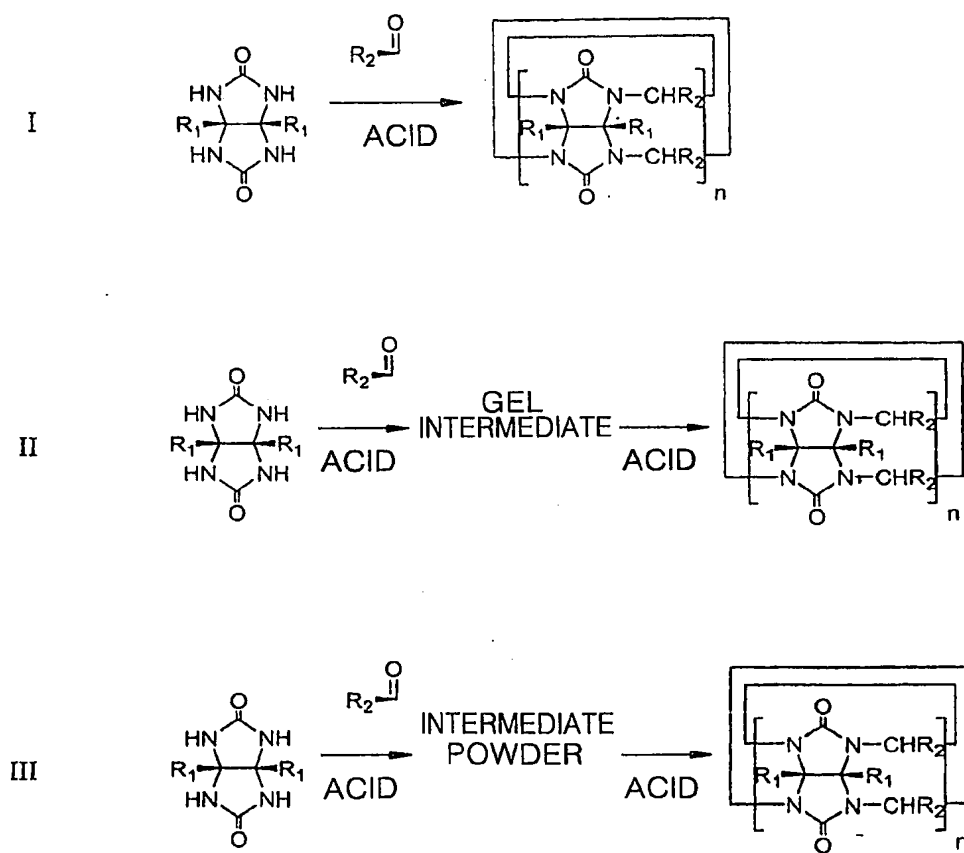
15 11. The pharmaceutical composition according to claim 10, wherein the metal complex of the formula 2 is an anticancer active component and the inclusion compound is used for treatment of cancer.

 12. The pharmaceutical composition according to claim 10,
20 wherein the inclusion compound is used for treatment of ovarian cancer, breast cancer or colonic cancer.

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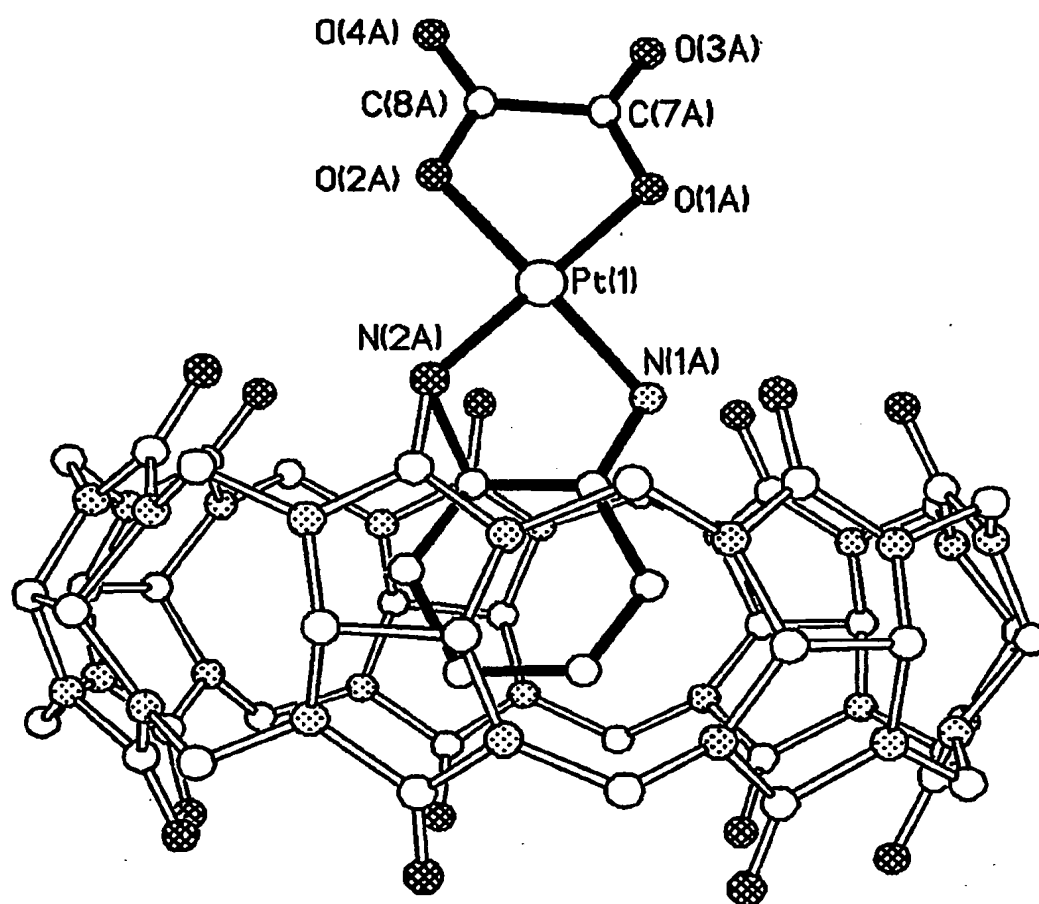
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FIG. 1



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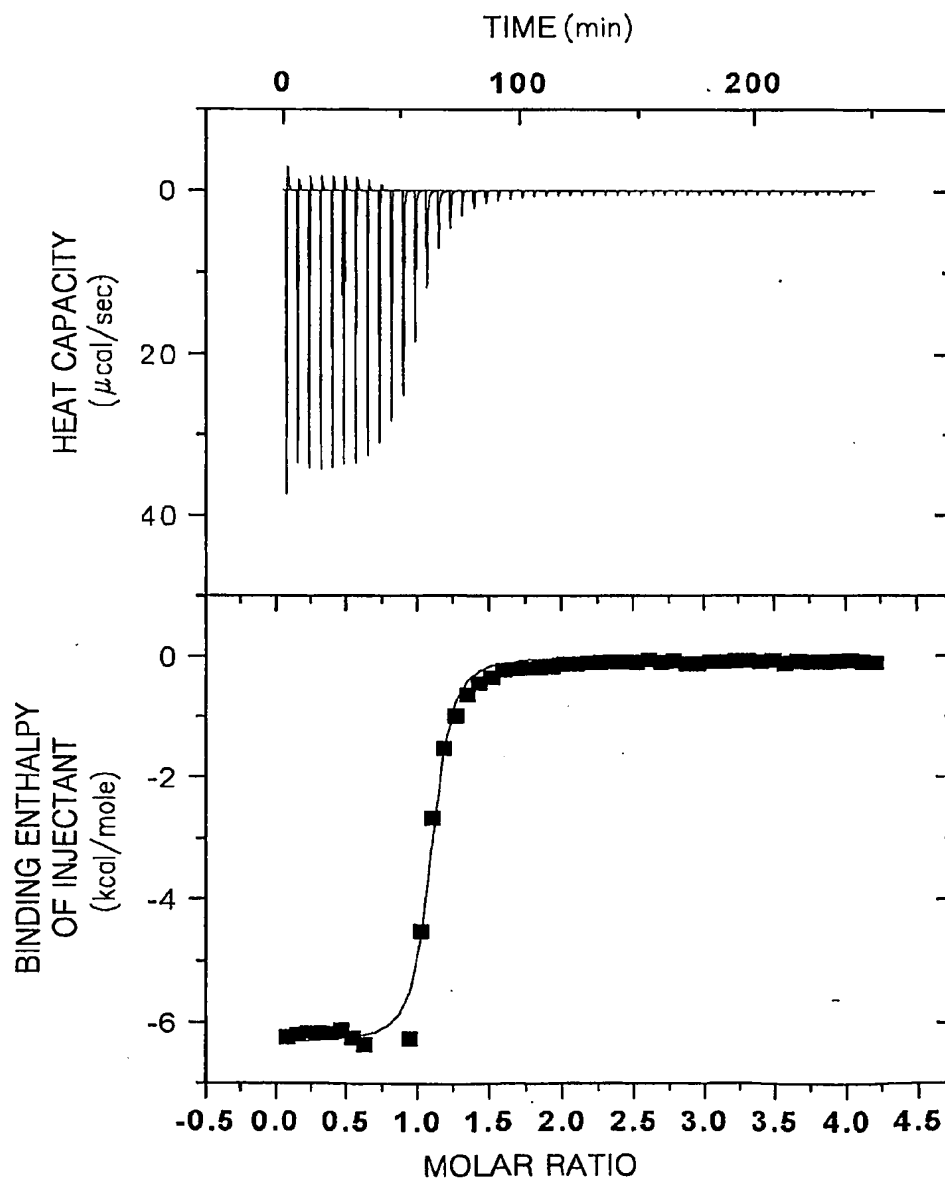
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FIG. 2



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FIG. 3



INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR02/01755

A. CLASSIFICATION OF SUBJECT MATTER**IPC7 C07F 5/00**

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7 C07F, C07D, C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
KR, JPO

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
STN(combination of structure and keyword search)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Biogioni, Mario et al, "Electronic attack of [I(py) ₂]+(NO ₃ -) on three-coordinate Pt0 precursors : Synthesis and In Vitro antitumor activity of water-soluble, five-coordinate Pt2 complexes", European J. of Inorganic Chemistry, 2000 (8), page 1717-1721, Wiley-VCH Verlag GmbH, 2000 see whole document	1-12
A	de Oliveira, M. B. et al, "New perfluorophthalate complexes of platinum(II) with chemotherapeutic potential", Metal-Based Drugs, 1996 3(3), page 117-122, Freund, 1996 see whole document	1-12
A	US 5965118 A (Acess Pharmaceuticals, Inc.) 12 Oct. 1999 see whole document	1-12
A	Beverly A. Teicher et al, "Combination of etanidazole with cyclophosphamide and platinum complexes", Cancer chemotherapy and Pharmacology, 1991 28(3), page 153-158, 1991 see whole document	1-12
A	Kim, Ui-Rak et al, "The study about interaction of cis-diaminedichloroplatin(cis-DDP) complexes with DNA base, 1-methylcytosine, for development of anti-tumor drugs", Tachan Hwahakhoe Chi, 1990 34(4), page 331-339, 1990 see conclusion -----	1-12

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family


Date of the actual completion of the international search

09 JANUARY 2003 (09.01.2003)

Date of mailing of the international search report

10 JANUARY 2003 (10.01.2003)

Name and mailing address of the ISA/KR

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Facsimile No. 82-42-472-7140

Authorized officer

PARK, Kil Chae

Telephone No. 82-42-481-5536



INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/KR02/01755

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5965118 A	12.10.1999	WO 9847537 A1	29.10.1998
		AU 736297 A1	13.11.1998
		EP 1009439 A1	21.6.2000
		JP 2001524098 T2	27.11.2001
		ZA 9803250 A	21.6.2000
-----End of Documents-----			